

<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b> (use as many sheets as necessary)				<b>Complete if Known</b>	
				Application Number	09/830,502
				Filing Date	October 29, 1999
				First Named Inventor	Barany et al.
				Art Unit	1652
				Examiner Name	R. Hutson
				Attorney Docket Number	19603/2615 (CRF D-2408)
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U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. <sup>1</sup>	U.S. Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number - Kind Code <sup>2</sup> (if known)			
	1	US-4,683,202	07/28/1987	Mullis	
	2	US-4,883,750	11/28/1989	Whiteley et al.	
	3	US-5,470,705	11/28/1985	Grossman et al.	
	4	US-6,576,453	06/10/2003	Barany et al.	
	5	US-6,054,564	04/25/2000	Barany et al.	
	6	US-5,494,810	02/27/1996	Barany et al.	
	7	US-5,496,699	03/05/1996	Sorenson	
	8	US-5,506,137	04/09/1996	Mathur et al.	
	9	US-5,516,663	05/14/1996	Backman et al.	
	10	US-5,728,526	03/17/1998	George, Jr. et al.	
	11	US-5,912,148	06/15/1999	Eggerding	
	12	US-6,312,892	11/06/2001	Barany et al.	
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FOREIGN PATENT DOCUMENTS						
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		Country Code <sup>3</sup> Number <sup>4</sup> Kind Code <sup>5</sup> (if known)				
	13	WO 91/17239	11/14/1991	WIPO		
	14	WO 98/03673	01/29/1998	WIPO		
	15	WO 00/26381	05/11/2000	WIPO		
	16	WO 97/31256	08/28/1997	WIPO		
	17	WO 97/45559	12/04/1997	WIPO		
	18	WO 93/17126	09/02/1993	WIPO		

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	19	Kreiner, T., "Rapid Genetic Sequence Analysis Using a DNA Probe Array System," <i>American Laboratory</i> 39-43 (March 1996)	
	20	Kovach et al., "Mutation Detection by Highly Sensitive Methods Indicates That p53 Gene Mutations in Breast Cancer Can Have Important Prognostic Value," <i>Proc. Natl Acad. Sci. USA</i> 93:1093-96 (1996)	
	21	Lin et al., "Multiplex Genotype Determination at a Large Number of Gene Loci," <i>Proc. Natl. Acad. Sci. USA</i> 93:2582-87 (1996)	
	22	Tavormina et al., "Thanatophoric Dysplasia (Types I and II) Caused by Distinct Mutations in Fibroblast Growth Factor Receptor 3," <i>Nature Genetics</i> 9:321-328 (1995)	
	23	Barany et al., "Cloning, Overexpression and Nucleotide Sequence of a Thermostable DNA Ligase-Encoding Gene," <i>Gene</i> 109:1-11 (1991)	
	24	Sidransky et al., "Identification of <i>ras</i> Oncogene Mutations in the Stool of Patients With Curable Colorectal Tumors," <i>Science</i> 256:102-105 (1992)	
	25	Brennan et al., "Molecular Assessment of Histopathological Staging in Squamous-Cell Carcinoma of the Head and Neck," <i>The New England Journal of Medicine</i> 332(7):429-35 (1995)	
	26	Berthélemy et al., "Identification of K- <i>ras</i> Mutations in Pancreatic Juice in the Early Diagnosis of Pancreatic Cancer," <i>Annals of Internal Medicine</i> 123(3):188-91 (1995)	
	27	Hayashi et al., "Genetic Diagnosis Identifies Occult Lymph Node Metastases Undetectable by the Histopathological Method," <i>Cancer Research</i> 54:3853-56 (1994)	
	28	Tada et al., "Detection of <i>ras</i> Gene Mutations in Pancreatic Juice and Peripheral Blood of Patients with Pancreatic Adenocarcinoma," <i>Cancer Research</i> 53:2472-74 (1993)	

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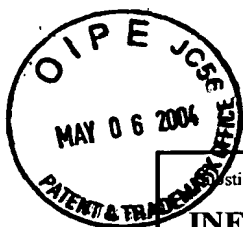
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	29	Tada et al., "Clinical Application of <i>ras</i> Gene Mutation for Diagnosis of Pancreatic Adenocarcinoma," <i>Gastroenterology</i> 100:233-38 (1991)	
	30	Mitsudomi et al., "Mutations of <i>ras</i> Genes Distinguish a Subset of Non-Small-Cell Lung Cancer Cell Lines From Small-Cell Lung Cancer Cell Lines," <i>Oncogene</i> 6:1353-62 (1991)	
	31	Day et al., "Detection of Steroid 21-Hydroxylase Alleles Using Gene-Specific PCR and a Multiplexed Ligation Detection Reaction," <i>Genomics</i> 29:152-62 (1995)	
	32	Frenkel et al., "Specific, Sensitive, and Rapid Assay for Human Immunodeficiency Virus Type 1 <i>pol</i> Mutations Associated With Resistance to Zidovudine and Didanosine," <i>J. Clin. Microbiol.</i> 33(2):342-47 (1995)	
	33	Abravaya et al., "Detection of Point Mutations With a Modified Ligase Chain Reaction (Gap-LCR)," <i>Nucleic Acids Research</i> 23(4):675-82 (1995)	
	34	Powell et al., "Molecular Diagnosis of Familial Adenomatous Polyposis," <i>The New England Journal of Medicine</i> 329(27):1982-87 (1993)	
	35	Jen et al., "Molecular Determinants of Dysplasia in Colorectal Lesions," <i>Cancer Research</i> 54:5523-26 (1994)	
	36	Redston et al., "Common Occurrence of APC and K- <i>ras</i> Gene Mutations in the Spectrum of Colitis-Associated Neoplasias," <i>Gastroenterology</i> 108:383-92 (1995)	
	37	Lu et al., "Quantitative Aspects of the Mutant Analysis by PCR and Restriction Enzyme Cleavage (MAPREC)," <i>PCR Methods and Applications</i> 3:176-80 (1993)	
	38	Kuppuswamy et al., "Single Nucleotide Primer Extension to Detect Genetic Diseases: Experimental Application to Hemophilia B (factor IX) and Cystic Fibrosis Genes," <i>Proc. Natl. Acad. Sci. USA</i> 88:1143-47 (1991)	

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	39	Rust et al., "Mutagenically Separated PCR (MS-PCR): A Highly Specific One Step Procedure for Easy Mutation Detection," <i>Nucleic Acid Research</i> 21(16):3623-29 (1993)	
	40	Suzuki et al., "Detection of <i>ras</i> Gene Mutations in Human Lung Cancers by Single-Strand Conformation Polymorphism Analysis of Polymerase Chain Reaction Products," <i>Oncogene</i> 5:1037-43 (1990)	
	41	Balles et al., "Facilitated Isolation of Rare Recombinants by Ligase Chain Reaction: Selection for Intragenic Crossover Events in the <i>Drosophila optomotor-blind</i> Gene," <i>Mol. Gen. Genet.</i> 245:734-40 (1994)	
	42	Reynolds et al., "Analysis of Genetic Markers in Forensic DNA Samples Using the Polymerase Chain Reaction," <i>Anal. Chem.</i> 63:2-15 (1991))	
	43	Buyse et al., "Rapid DNA Typing of Class II HLA Antigens Using the Polymerase Chain Reaction and Reverse Dot Blot Hybridization," <i>Tissue Antigens</i> 41:1-14 (1993)	
	44	Gyllensten et al., "PCR-Based HLA Class II Typing," <i>PCR Meth. Appl.</i> 1:91-98 (1991)	
	45	Chamberlain et al., "Deletion Screening of the Duchenne Muscular Dystrophy Locus Via Multiplex DNA Amplification," <i>Nucleic Acids Res.</i> 16:11141-56 (1988)	
	46	Tsui, L. C., "Mutations and Sequence Variations Detected in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Gene: A Report From the Cystic Fibrosis Genetic Analysis Consortium," <i>Human Mutat.</i> 1:197-203 (1992)	
	47	Hollstein et al., "p53 Mutations in Human Cancers," <i>Science</i> 253:49-53 (1991)	
	48	Saiki et al., "Enzymatic Amplification of $\beta$ -Globin Genomic Sequences and Restriction Site Analysis for Diagnosis of Sickle Cell Anemia," <i>Science</i> 230:1350-1354 (1985)	

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	49	Wu et al., "The Ligation Amplification Reaction (LAR) -- Amplification of Specific DNA Sequences Using Sequential Rounds of Template-Dependent Ligation," <i>Genomics</i> 4:560-69 (1989)	
	50	Landegren et al., "A Ligase-Mediated Gene Detection Technique," <i>Science</i> 241:1077-80 (1988)	
	51	Winn-Deen, et al., "Sensitive Fluorescence Method for Detecting DNA Ligation Amplification Products," <i>Clinical Chemistry</i> 37(9):1522-23 (1991)	
	52	Barany, F., "Genetic Disease Detection and DNA Amplification Using Cloned Thermostable Ligase," <i>Proc. Nat'l Acad. Sci. USA</i> 88:189-93 (1991)	
	53	Grossman et al., "High-Density Multiplex Detection of Nucleic Acid Sequences: Oligonucleotide Ligation Assay and Sequence-Coded Separation," <i>Nucl. Acids Res.</i> 22(21):4527-34 (1994)	
	54	Jou et al., "Deletion Detection in the Dystrophin Gene by Multiplex Gap Ligase Chain Reaction and Immunochromatographic Strip Technology," <i>Human Mutation</i> 5:86-93 (1995)	
	55	Gibbs et al., "Detection of Single DNA Base Differences by Competitive Oligonucleotide Priming," <i>Nucleic Acids Res.</i> 17:2437-48 (1989)	
	56	Chehab et al., "Detection of Specific DNA Sequences by Fluorescence Amplification: A Color Complementation Assay," <i>Proc. Natl. Acad. Sci. USA</i> 86:9178-82 (1989)	
	57	Livak et al., "Detection of Single Base Differences Using Biotinylated Nucleotides With Very Long Linker Arms," <i>Nucleic Acids Res.</i> 20(18):4831-37 (1992)	
	58	Nickerson et al., "Automated DNA Diagnostics Using an ELISA-Based Oligonucleotide Ligation Assay," <i>Proc. Natl. Acad. Sci. USA</i> 87:8923-27 (1990)	

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	59	Dong et al., "Mutational Studies of Human DNA Polymerase $\alpha$ ," <i>J. Biol. Chem.</i> 268(32):24175-24182 (1993)	
	60	Copeland et al., "Fidelity Studies of the Human DNA Polymerase $\alpha$ ," <i>J. Biol. Chem.</i> 268(15):11041-11049 (1993)	
	61	Reha-Krantz et al., "Motif A of Bacteriophage T4 DNA Polymerase: Role in Primer Extension and DNA Replication Fidelity," <i>J. Biol. Chem.</i> 269(8):5635-5643 (1994)	
	62	Eggerding, F., "A One-Step Coupled Amplification and Oligonucleotide Ligation Procedure for Multiplex Genetic Typing," <i>PCR Methods and Applications</i> 4:337-345 (1995)	
	63	Friedhoff et al., "Quantitative Polymerase Chain Reaction with Oligodeoxynucleotide Ligation Assay/Enzyme-Linked Immunosorbent Assay Detection," <i>Anal. Biochem.</i> 215:9-16 (1993)	
	64	Wallace et al., "Ligase Chain Reaction for the Detection of Specific DNA Sequences and Point Mutations," in Pfeifer, ed., <i>Technologies for Detection of DNA Damage and Mutations at 307-322</i> , Plenum Press, New York, NY (1996)	
	65	Reyes et al., "Ligase Chain Reaction Assay for Human Mutations: The Sickle Cell by LCR Assay," <i>Clinical Chemistry</i> 43(1):40-44 (1997)	
	66	Jónsson et al., "Sequence of the DNA Ligase-Encoding Gene from <i>Thermus scotoductus</i> and Conserved Motifs in DNA Ligases," <i>Gene</i> 151:177-180 (1994)	
	67	Luo et al., "Improving the Fidelity of <i>Thermus thermophilus</i> DNA Ligase," <i>Nucleic Acids Res.</i> 24:3071-3078 (1996)	
	68	Luo et al., "Identification of Essential Residues in <i>Thermus thermophilus</i> DNA Ligase," <i>Nucleic Acids Res.</i> 24:3079-3085 (1996)	
	69	Tong et al., "Biochemical Properties of a High Fidelity DNA Ligase from <i>Thermus</i> Species AK16D," <i>Nucleic Acids Research</i> 27:788-794 (1999)	
	70	Zirvi et al., "Ligase-Based Detection of Mononucleotide Repeat Sequences," <i>Nucleic Acids Research</i> 27(24):e40i-e40viii (1999)	
	71	Ngo et al., "Computational Complexity, Protein Structure Prediction, and the Levinthal Paradox," in <i>The Protein Folding Problem and Tertiary Structure Prediction</i> , Merz et al., Eds., Boston, MA: Birkhauser, Chapter 14, pp. 491-495 (1994)	

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	72	Takahashi et al., "Purification of HB8 DNA Ligase by Red Sepharose Chromatography," <i>Agric. Biol. Chem.</i> 50(5):1333-1334 (1986)	
	73	Takahashi, M., et al., "Thermophilic DNA Ligase Purification and Properties of the Enzyme from <i>Thermus Thermophilus</i> HB8," <i>Biol. Chem.</i> 259(16):10041-10047 (1984)	
	74	Takahashi, M., et al., "Thermophilic HB8 DNA Ligase: Effects of Polyethylene Glycols and Polyamines on Blunt-End Ligation of DNA, <i>J. Biochem.</i> , 100:123-31 (1986)	
	75	Belgrader et al., "A Multiplex PCR-Ligase Detection Reaction Assay for Human Identity Testing," <i>Genome Science &amp; Tech.</i> 1:77-87 (1996)	
	76	Newton, "The Production of PCR Products with 5' Single-Stranded Tails Using Primers That Incorporate Novel Phosphoramidite Intermediates," <i>Nucleic Acids Research</i> 21(5): 1155-1162 (1993)	

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